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Regioselective Hydroxylation in the C Ring of \textit{ent}-Kaurene; Syntheses of \textit{ent}-11α-Hydroxykaurene and \textit{ent}-11α-Hydroxykauren-15-one

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Regioselective hydroxylation at the C–11 position of \textit{ent}-kaurene (5) was achieved via radical cyclization of the hydroxy group at the C–17 position. Naturally occurring \textit{ent}-11α-hydroxykauren-15-one (3) was synthesized from the hydroxylated kaurene 4 in two steps.

KEY WORDS: Hydroxylation/ \textit{ent}-Kaurene/ \textit{ent}-11α-Hydroxykaurene/ \textit{ent}-11α,15β-Dihydroxykaurene/ \textit{ent}-11α-Hydroxykauren-15-one/ Radical Cyclization/ Lead Tetraacetate/ Tosylhydrazone/

In the course of our investigation on the physiologically active diterpenoids, we found that \textit{ent}-15β-hydroxykaur-16-ene (1) had a potent stimulating effect on corticosterone production in isolated rat adrenal cells\textsuperscript{1} and that poly hydroxylated kaurenoids such as oridonin (2) showed strong antitumor activity against Ehrlich ascites carcinoma in mice.\textsuperscript{2} These findings stimulated our interest into investigating the steroidogenic effect of various hydroxykaurenes and the antitumor effect of various hydroxykaurenones, because it is anticipated that the hydroxy group in the kaurene skeleton plays an important role in the action of physiologically active kaurenoids.

In order to prepare various hydroxykaurenoids, we recently succeeded in regioselective hydroxylations of the unactivated carbon atoms (C–7, –9, –12 and –14) on the B and C rings in the kaurene skeleton through radical cyclization of a hydroxymethyl group on the D ring.\textsuperscript{3} Though a report concerning the hydroxylation of the C–11 position on the kaurene has already been published by Kato and coworkers,\textsuperscript{4} the synthetic method for the preparation of \textit{ent}-11α-hydroxykauren-15-one (3) by Kato requires comparatively long synthetic steps (total 11 steps...
from kaurene). No report on the synthesis of ent-11α-hydroxykauren-15-one (3) and ent-11α-hydroxykaurene (4) from ent-kaurene (5).

A method for the transformation of kaurene (5) into the lactone 6 was published by McCrindle\(^5\) and Kato,\(^4\) respectively (Scheme I). However, radical cyclization of the alcohol 7 into the cyclic ether 8 proceeded in a yield of less than 41% according to their method. The yield was improved to 80% by the use of the modified reaction conditions (See experimental section).

The transformation of the lactone 6 into the hydroxykaurenone 3 via 4 is shown in Scheme II. Thus, reduction of the lactone 6 with diisobutyl aluminum hydride gave a mixture of epimeric hemiacetals 9, which was converted to the tosylhydrazone 10 in 70% overall yield by the treatment with tosylhydrazone in the presence of acetic acid. The configuration of hydrazone moiety in the structure of 10 was considered to be a β-configuration because the torsional strain between the 13-hydrogen and the 17-carbon atom\(^6\) prevents the inversion of the configuration from β to α under the reaction conditions. The attempted Shapiro reaction\(^7\) on the hydrazone 10 with n-butyl lithium (excess) did not afford the desired kaurenol 4, but the butylated product 11.\(^8\) On the other hand, use of lithium diisopropylamide which is a non-nucleophilic base gave the intended product 4 in low yield (16%). Several non-nucleophilic bases were tried to improve the yield without success.
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Allylic oxidation of kaurenol 4 by Sharpless method\textsuperscript{9} proceeded smoothly to give dihydroxykaurene 12 resulting from the less hindered \( \alpha \)-side attack of the reagent. Subsequent oxidation of the allylic alcohol 12 with manganese dioxide afforded the \( \alpha,\beta \)-unsaturated ketone 3, which was identified with naturally occurring \textit{ent}-11\( \alpha \)-hydroxykauren-15-one\textsuperscript{10} by the comparison of the spectroscopic data.

Investigation of the physiological activity of synthesized 11-hydroxykaurene and its derivatives is now in progress.

**EXPERIMENTAL SECTION**

Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer or a JASCO A-202 spectrophotometer, and \( ^1 \text{H} \)-NMR spectra were obtained with JEOL FX-400 spectrometer. Chemical shift are reported relative to internal tetramethylsilane. Mass spectra (MS) were determined on a JEOL JMS-O1SG double-focusing mass spectrometer or a JEOL JMS-DX 300 mass spectrometer. Melting points were determined with a Yanagimoto apparatus and are uncorrected.

\textit{ent}-kaurene (5) isolated from the leaves of \textit{Cryptomeria japonica}\textsuperscript{11} was converted to the kauranol 7 by the hydroboration-oxidation reaction.\textsuperscript{1-1}

Radical Cyclization of Kauranol 7 with Lead Tetraacetate

A solution of 7 (301 mg) and lead tetraacetate (12.5 g) in dry cyclohexane was stirred with refluxing under irradiation with 100 W tungsten lamp until kauranol on TLC disappeared (ca. 2.5 h). After filtration, the residue was washed with ether. The combined organic layer was washed with aqueous sodium thiosulfate and brine successively. After being dried over \( \text{Na}_2\text{SO}_4 \), the solvent was evaporated \textit{in vacuo} and the residue was chromatographed on silica gel column to give the cyclic ether 8 (249 mg, 80% yield).\textsuperscript{5}

\textit{ent}-(16R)-Kauran-17,11\( \alpha \)-olide (6)

To a solution of 8 (4.51 g) in a mixture of carbon tetrachloride (35 ml) and acetonitrile (35 ml) were added aqueous sodium periodate (13.5 g in 50 ml water) and ruthenium trichloride (32 mg). The mixture was vigorously stirred for 2.5 h at room temperature. After being quenched with \( \text{iso} \)-propanol to destroy remaining \( \text{RuO}_4 \), the reaction mixture was diluted with water. The extract with dichloromethane was treated as usual to give a crude product, which was chromatographed on silica gel column to afford lactone 6\textsuperscript{5} (4.25 g, 90% yield), mp 177–178°C.

Tosylhydrazone 10

To a solution of 6 (45.8 mg) in dry tetrahydrofuran (2.5 ml) was added hexane solution (2.5 ml) of 20% diisobutylaluminium hydride, and the mixture was stirred for 1 h at 0°C. After being quenched with water, the reaction mixture was filtered with celite. The filtrate was evaporated to give a crude crystalline product (72 mg) which contained epimeric mixture of 9. To a solution of the crude 9 dissolved in dichloromethane (1 ml) and acetic acid (1 ml) was added tosylhydrazone (83 mg) and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was then poured into cold aqueous solution of sodium bicarbonate. Usual
work up including extraction with ethyl acetate gave a crude material (126.5 mg) which was chromatographed on the silica gel column to yield tosylhydrazone 10 (50.7 mg, 70%), colorless powder from hexane — ethyl acetate, mp 161.5—162.5°C. IR$\nu_{\text{max}}$ cm$^{-1}$ (CHCl$_3$): 3320, 1714 and 1610. $^1$H-NMR $\delta$ (CDCl$_3$): 7.81, 7.30 (each 2H, q of AB type, J=8 Hz, Aromatic-H), 6.40 (1H, s, N-H), 4.26 (1H, d, changed to singlet by D$_2$O, J=11 Hz, 11-H), 4.06 (1H, s, 17-H), 3.85 (1H, d, J=11 Hz, -OH), 2.43 (3H, s, Ar-CH$_3$), 0.92, 0.85 and 0.81 (each 3H, s, 3×CH$_3$). Anal. Calcd for C$_{27}$H$_{40}$O$_3$N$_2$S: C, 68.61; H, 8.51; N, 5.93. Found: C, 68.93; H, 8.65; N, 5.91.

**Shapiro Reaction with Tosylhydrazone 10**

To a solution of 10 (20.3 mg) in dry ether (1.5 ml) was added n-butyl lithium (1.5 M THF solution, 0.25 ml) and the mixture was stirred at room temperature for 1 h. Usual work up of the extract gave a crude substance which was chromatographed on the silica gel column to give butyulated compound 11 (10.1 mg, 67%) as oil. IR$\nu_{\text{max}}$ cm$^{-1}$ (CHCl$_3$): 3600, 3450, 1455, 1395 and 965. $^1$H-NMR $\delta$ (CDCl$_3$): 3.86 (1H, d, J=6.6 Hz, 11-H), 2.03 (1H, m), 0.88, 0.85 and 0.78 (each 3H, s, 3×CH$_3$). High-resolution MS $m/z$: 346.3234. Found: 346.3233.

**ent-11α-Hydroxykaurene (4)**

To a solution of tosylhydrazone 10 (23.1 mg) in dry ether (1 ml) was added an ether solution of lithium diisopropylamid (0.75 M, 0.5 ml) and the mixture was stirred at room temperature for 1.5 h. Usual work up of the extract gave a crude substance, which was chromatographed on the silica gel column to separate kaurenol 4 (2.3 mg, 16%), colorless powder from methanol — ethyl acetate, mp 131-132°C. $^1$H-NMR $\delta$ (CDCl$_3$): 5.03, 4.85 (each 1H, s, 17-H$_2$), 3.87 (1H, br s, 11-H), 2.70 (1H, br s, 13-H), 0.90, 0.88 and 0.81 (each 3H, s, 3×CH$_3$). MS $m/z$: 288 (M$^+$), and 270 (M$^+$-H$_2$O).

**ent-11α,15β-Dihydroxykaurene (12)**

To a solution of SeO$_2$ (11.0 mg) in CH$_2$Cl$_2$ (1 ml) was added 75 μl of 70% aqueous tert-butyl hydroperoxide. After the mixture had been stirred for 1 h at room temperature, a solution of kaurenol 4 (50 mg) in dichloromethane (3 ml) was added and the mixture was stirred for 1.5 h at room temperature. After being quenched with aqueous sodium thiosulphate, usual work up of the extract gave an oily substance (70.8 mg), which was chromatographed on a silica gel column to give diol 12 (38 mg, 76%), colorless needles (from hexane). mp 192.5–193.2°C. IR$\nu_{\text{max}}$ cm$^{-1}$: 3650. $^1$H-NMR $\delta$ (CDCl$_3$): 5.27, 5.25 (each 1H, s, 17-H$_2$), 4.26 (1H, s, 15-H), 3.88 (1H, d, J=5.1 Hz, 11-H), 2.78 (1H, br s, 13-H), 0.92, 0.89 and 0.82 (each 3H, s, 3×CH$_3$). High-resolution MS $m/z$: M$^+$ Calcd for C$_{20}$H$_{32}$O$_2$: 304.240. Found: 304.238.

**ent-11α-Hydroxykauren-15-one (3)**

To a solution of 12 (9.2 mg) in CH$_2$Cl$_2$ (1 ml) was added manganese dioxide (49.8 mg) and the mixture was stirred for 3 days at room temperature. After filtration, the residue was washed with dichloromethane. The combined solution was evaporated off to give a residue which was chromatographed on a silica gel column to separate crystalline ketone 3 (3.4 mg,
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The obtained ketone 3 was identified as ent-11α-hydroxykauren-15-one by the comparison of the IR and 1H-NMR data.

REFERENCES AND NOTES


(8) In the reaction of tosylhydrazone with alkyllithium, substitution occasionally competes with elimination (see ref. 7).


(12) J. R. Hanson, Tetrahedron, 1967, 73, 801.